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Unrelated donors for hematopoietic stem cell transplantation in the People's Republic of China

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Abstract

The number of hematopoietic stem cell transplantations (HSCT) in China has increased dramatically, especially since the late 1990s. As the one child policy has been implemented in China, more and more alternative donors such as unrelated donors (URD) have been used for patients who need transplantation without a human leukocyte antigen (HLA) identical sibling donor. A dramatic increase in the number of URD-HSCTs performed in China was observed after the Chinese Marrow Donor Program started servicing the public in 2001, resulting in the rapid expansion of the donor pool. The most common indication is hematological malignancies in URD-HSCT. Advances in HLA-typing techniques, a reduced intensity conditioning regimen, and prophylaxis strategy for GVHD have greatly improved the outcome and expanded patient eligibility for URD-HSCT. With rapid the economic development in China there will be much development potential for HSCT.

Keywords: hematopoietic stem cell transplantation, HSCT, unrelated donor

Introduction

The first allogeneic bone marrow transplantation (BMT) in the People's Republic of China (P.R.C.) was successfully performed in an acute leukemia patient at Peking University People's Hospital by D-P Lu in 1981. Since then the number of hematopoietic stem cell transplantations (HSCT) in China has increased gradually, especially since the late 1990s. Now, more than 2000 HSCTs per year including 1000 allogeneic HSCTs (allo-HSCTs), have been performed in recent years in more than 50 BMT units in mainland China [1]. As the one child policy has been in effect in China for 30 years, unrelated donors (URD) represent one of the common alternative sources of stem cells for allo-HSCT.

1. Sources of unrelated donors

Unrelated donors for allo-HSCT in the P.R.C. are from the Chinese Marrow Donor Program (CMDP) and the Taiwan Tzu Chi Stem Cell Center. The Taiwan Tzu Chi Stem Cell Center was established in 1993, and the first stem cell donation to mainland China was carried out in 1997. As the CMDP only started service for the public in 2001, before 2001 unrelated donors for allo-HSCT in mainland China were mainly from the Taiwan Tzu Chi Stem Cell Center. By the end of June 2010, the number of donors had risen to 333,798 and 927 stem cells had been successfully donated to mainland China. The primary three BMT units in mainland China, ordered by the number of stem cell donations received from the Taiwan Tzu Chi Stem Cell Center, are the First Affiliated Hospital of Zhejiang University School of Medicine (215 cases), Guangzhou Nanfang Hospital (145 cases), and Beijing Daopei Hospital (66 cases) [2].

The CMDP was established in 1992 and started service for

the public in 2001. The CMDP is responsible for organization and mobilization of volunteers, searching for donors, standardization of HLA typing, and the promotion of research on clinical transplantation in China. At the end of 2009, the CMDP comprised 31 branch registries, 31 HLA-typing laboratories, five high-resolution laboratories and one quality control laboratory [3].

The first search requests for donors from the CMDP were processed in 1996 and the first transplant was facilitated successfully in September 1996. The total number of donor registrations has increased dramatically since 2002. In 2002, the CMDP only had 6,000 donors. By the end of May 2010, the number of donors had risen to 1,130,566, and 1,662 stem cell donations and 16,659 search requests had been carried out [3]. The CMDP is currently the largest donor pool among the nine Asian countries/regions and the third largest register of unrelated donors in the world. It is expected that the number of donor registrations in the CMDP will reach 2,000,000 in 2015. There are more than 200 search requests per month with a 60% preliminary matching rate. The processing of HLA data systems has made significant enhancements for more efficient and accurate alternative donor searches, and the median time to identify a suitable URD is now about 2 months. The CMDP also cooperates with the major cord blood banks in mainland China. There are over 30,000 units of cord blood available for search requests in the CMDP [4]. The CMDP is actively involved in international cooperations. More than 300 preliminary searches from more than 20 countries have been carried out. Stem cells from the CMDP have been successfully donated to the United States, Singapore, Switzerland, Korea, and the United Kingdom.

2. Current URD-HSCT activity

2.1. Number of URD-HSCTs

The number of URD-HSCTs has been increasing in China since 2000. A survey of 16 BMT units in mainland China from 1986 to 2005 indicates that the predominant types of transplantation performed are identical sibling (36%), related mismatched/ haploidentical (11.2%), unrelated (7.5%), and autologous (44.5%) [5]. The report from the Asia-Pacific Blood and Marrow Transplantation Group showed that of 352 HSCTs performed in mainland China in 2006, 60% were identical sibling and related mismatched/haploidentical, 20% were unrelated, and 20% were autologous [6]. The data submitted to the Chinese Hematopoietic Stem Cell Transplantation Committee from 30 BMT units from June 2007 to June 2008 indicated that of 1099 allo-HSCTs, 533 (48.5%) were identical sibling, 345 (31.4%) were related haploidentical, 207 (18.8%) were unrelated, and 14 (1.3%) were cord blood.

2.2. Disease indication

The most common indication for URD-HSCT is hematological malignancies. Follow-up surveys were completed on 822 CMDP stem cell recipients between 1996 and 2007. The distribution of disease entities and prevalent diseases being transplanted is CML (35.9%), ALL (29.2%), AML (18.6%), MPD (3.3%), and lymphoid malignancy (2.9%) [4]. The number of transplants for CML has decreased in most Asia countries/regions since 2000, excluding China and Iran [6]. Allo-HSCT is still the main therapy for 15% or more of current patients in China [7]. Wang J.X. et al [8] analyzed 1,824 CML patients from 15 hospitals throughout China in the whole year of 2005 and 22.72% received allo-HSCT. The reasons may be the following factors: CML in China tends to afflict a younger population than in Western countries, due to restriction of financial support, only one third of CML patients were treated with imatinib, and the majority of those treated were not monitored in time.

2.3. Clinical outcomes of URD-HSCT

With advances in HLA-typing techniques, transplant techniques, and supporting care, the clinical outcome of URD-HSCT has been improved. The data from the CMDP showed the 1-year overall survival (OS) of stem cell recipients was 53% in 2004, 60% in 2005, 65% in 2006, and 71% in 2007 [4]. Follow-up surveys of 182 patients receiving URD-HSCT at the Beijing Daopei Hospital from September 2003 to February 2010 indicated the 5-year OS was 72.2%, and the disease free survival (DFS) was 64.9% [9].

3. Advances in URD-HSCT

Despite the improvements in transplant procedures, URD-HSCT is still associated with a higher treatment-related mortality (TRM) due to the toxicity of conditioning regimens, severe GVHD, and infectious complications. Non-relapse mortality (NRM) rates over 50% are commonly reported in patients over 40 years old [10].

3.1. Conditioning regimens

The main myeloablative conditioning regimens used in URD-HSCT in China are busulfan/cyclophosphamide (BuCy) or BuCy combined with cytarabine without total body irradiation. A significant trend has been an increase in the numbers of transplants in patients over the age of 50 years because of the introduction of reduced intensity conditioning (RIC) regimens. From 1996 to 2007, 4% (34 of 822 transplants) of CMDP stem cell recipients were ≥50 years old [4]. RIC regimens were predominantly fludarabine-based combinations without irradiation.

The BMT Center of the First Affiliated Hospital of Zhejiang University School of Medicine [11] first performed RIC URD-HSCT combined with imatinib in 18 CML patients in the first chronic phase (CP1). The conditioning regimen included Flu, Bu and antithymocyte globulin (ATG). Imatinib was administered for 3–6 months before transplantation to reduce leukemia burden and after transplantation to treat relapsed disease or graft failure. Prophylactic imatinib was commenced on day +100 in engrafted patients to prevent relapse and was discontinued 12 months after transplantation. Overall survival was 82.1% and complete molecular remission was 91.3%. The results suggested that RIC allo-SCT combined with imatinib was well tolerated in CML patients with a low-risk of GVHD. Imatinib changed the kinetics of disease relapse after RIC allo-SCT and the anti-leukemic immunological function of RIC could provide a definite cure for CML.

3.2. Prophylaxis regimens for aGVHD

Acute GVHD remains a significant cause of transplant-related mortality and morbidity following allo-HSCT, and especially following URD-HSCT. The combination of calcineurin inhibitor (cyclosporine) and methotrexate is the standard prophylaxis regimen for GVHD. Many BMT units in China add ATG to this standard prophylaxis regimen in URD-HSCT. Due to a high incidence of infection in prophylaxis with ATG, Huang H et al [12] firstly used a combination of cyclosporine, methotrexate and low-dose, short-course mycophenolate mofetil (MMF) for GVHD prophylaxis in 12 patients receiving URD-HSCT, including 8 patients with HLA-A, B,DRB1 matched, 3 patients with one mismatched allele and one patient with two mismatched alleles. Only one patient developed grade IV aGVHD and two patients developed grade II aGVHD, who achieved complete remission after being treated with the combination of MMF, methylprednisolone and CsA. They used this prophylaxis regimen in 138 URD-HSCT recipients from January 2001 to March 2009, the cumulative incidences of severe (grade III–IV) aGVHD, chronic GVHD (cGVHD) and extensive cGVHD were 10.9%, 32.6%, and 15.9% [13]. The cumulative incidences of severe aGVHD, cGVHD, and extensive cGVHD were 8.6%, 32.9%, and 13.7% in URD-HSCT recipients receiving cyclosporine, methotrexate, and ATG for GVHD prophylaxis in the Institute of Hematology of People's Hospital of Peking University from September 2002 to April 2008 [14]. The two regimens are similar in reducing GVHD, which suggests that MMF could be used effectively and safely for prevention of aGVHD in URD-HSCT.

4. Trends and perspective for HSCT in China

The Asia-Pacific Blood and Marrow Transplantation Group [6] surveyed HSCT activity in nine Asian countries/regions from 1986 to 2006. The results showed the most significant increases in the past 10 years were observed in Iran and China. The ratio of the reported numbers of HSCTs in year 2006 and in year 1996 was 10.2 in Iran and 9.8 in China. However, even in countries/regions within the high-income group (Hong Kong, Japan, Korea, and Singapore) the number of HSCTs performed has been consistently increasing in the study period and is not likely to reach a plateau any time soon. This suggests that the demand for HSCTs has not been fulfilled in any of these countries.

The significant effect of the economic strength of individual countries on HSCT activity was reported by Gratwohl et al [15]. Recently, a retrospective survey study of HSCTs for the year 2006 collected by 1,327 centers in 71 participating countries of the Worldwide Network for Blood and Marrow Transplantation showed the gross national income per capita was found to have the highest associations with HSCT rates. The median HSCT rates (total numbers of HSCTs per 10 million population) varied between regions and countries: 184 (range, 0.6–488.5) in Asia, and 268.9 (range, 5.7–792.1) in Europe. Their results suggested HSCT is used for a broad spectrum of indications worldwide, but most frequently in countries with higher gross national incomes, higher governmental health care expenditures, and higher team densities [16].

According to the World Bank's income category based on the Gross National Income per capita, China is a lower-middle-income country. The data from Asia-Pacific Blood and Marrow Transplantation Group indicated numbers of transplant institutes per 100 million population was 1 in China and the highest was 279 in Japan; numbers of reported HSCTs per 100 million population was 3 in China and the highest was 301 in Japan [6]. With rapid economic development in China, there will be much development potential for HSCT, especially in some economic high-income areas.

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Ссылка: Клеточная терапия и трансплантация, том 3, номер 10

Неродственные доноры при трансплантации гемопоэтических стволовых клеток в Китайской Народной Республике

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Резюме

Число трансплантаций гемопоэтических стволовых клеток (ТГСК) в Китае резко возросло, особенно по сравнению с концом 90-х годов. Поскольку в Китае введена политика „одна семья-один ребенок“, все больше альтернативных доноров, например, неродственных (НРД), привлекаются для лечения больных, требующих трансплантации и не имеющих HLA-идентичного донора из числа сибсов. Значительное возрастание числа неродственных ТГСК, проводимых в Китае, отмечено после того, как в 2001 году было официально начато обслуживание по китайской Программе доноров костного мозга, что привело к быстрому росту пула доноров. Наиболее частым показанием для неродственной ТГСК являются онкогематологические заболевания. Успехи в технологии HLA-типирования, сниженние интенсивности режимов кондиционирования и стратегии профилактики РТПХ в большой мере улучшили исходы и расширили пригодность неродственной ТГСК для пациентов. По мере быстрого экономического развития Китая, будет больше возможностей для развития потенциала ТГСК.

Ключевые слова: трансплантация гемопоэтических стволовых клеток, ТГСК, неродственные доноры, Китай